Question #1: What evidence is there to conclude that there is or is not a threshold effect for cancer, heart disease, adverse reproductive effects or lung disease caused by exposure to tobacco or tobacco smoke, and what is the threshold level, if it exists?

Response #1:

There is no generally agreed safe level of smoking based on the epidemiological data available to date. However, conceptually, thresholds are conceivable but may not be seen due to the complexity of the exposure and the disease processes as well as a lack of resolution of the epidemiological dosimeter. This situation might change with new products featuring a less complex aerosol composition and better tools to determine the actual exposure in epidemiological studies. Generally, any reduction in exposure is regarded advantageous regardless of the presence of thresholds.

In the following, the question of thresholds for smoking-related diseases will be discussed based on epidemiological and mechanistic grounds using the data available on the effects of smoking existing cigarette types.

The 'gold standard' for the determination of the existence of a threshold in the dose-response relationship of a disease is certainly epidemiology. However, the determination of thresholds requires a reasonable resolution of the dosimeter, and this dosimeter should be based on actual exposure data. In terms of the cigarette smoke dose, epidemiology has been mainly based on self- or surrogate-reported numbers of cigarettes smoked per day. Most epidemiological studies have used increments of 10 cigarettes per day, which is, of course, relative to the current average consumption in the US of 19 cigarettes per day. In addition, this dosimeter does not consider the large impact of smoking behavior, e.g., degree of inhalation (up to 2-fold differences in the lung cancer mortality ratio, US DHHS, 1989), that is variable for individual smokers and may be different between exposure categories.

With the limitations in dose resolution given, there is no indication for a non-linear dose-response relationship for lung cancer in the lower-dose range (e.g., US DHHS 1982 and 1989; IARC, 1986). The same holds true for other cancer types that are also related to cigarette smoking, e.g., bladder cancer (Stellman, 1986). For cardiovascular diseases, the dose-response relationship has been claimed to be relatively flat. Law et al. (1997) cite a relative risk of 1.78, at age 65, for the association of cardiovascular disease with smoking 20 cigarettes per day. By extrapolation, they also calculate a pooled relative risk of 1.39 based on five studies that presented data for the association of cardiovascular disease with the smoking of one cigarette per day. A similar pattern can be observed for the coronary heart disease mortality ratios comprised by the US DHHS (1983). For myocardial infarction, however, the US DHHS (1983) reported a supra-linear or concave dose-response relationship; however, the data did not suggest a threshold. For chronic bronchitis and emphysema, with the above-mentioned limits of resolution, there is no indication of deviations from linear dose-response relationships (US DHHS, 1984). For reprotoxicological effects, only rough dose-response data are available that generally do not allow any conclusion on the presence or absence of thresholds (e.g., US DHHS, 1980). In conclusion, the current epidemiological methods are not accurate enough to prove or disprove a no-effect threshold for cigarette smoke-related diseases.

However, there is convincing epidemiological evidence that lower smoke exposure leads to lower risk, whether or not a hypothetical threshold exists.

From a mechanistic point of view, thresholds are generally conceivable. Non-linear dose-response relationships were established for some cancers in humans, e.g., radiation-induced sarcoma (Chemelevsky et al., 1986). Consequently, the current paradigm of default linear dose-response relationships in genotoxic carcinogenesis has been questioned (e.g., Purchase, 1998; Zenick and Bogdanffy, 2000; Müller and Kasper, 2000). This seems to be reasonable for mutagenic and more so for clastogenic effects in face of respective detoxification and repair systems. Moreover, for non-genotoxic carcinogenesis and the promotion phase of carcinogenesis, non-linear dose-response relationships without or with thresholds have been conceptually accepted. For instance, the role of cell proliferation in carcinogen-induced tumor formation leading to threshold effects in some target organs was demonstrated in animal models (Poirier and Beland, 1992). The weight of genotoxic versus non-genotoxic events in tobacco smoke-related carcinogenesis, in particular in the lungs, has been discussed. The declining risk with the duration since smoking cessation (Stellman, 1986; US DHHS, 1989) has been taken as strong evidence for a major role of promotion in pulmonary carcinogenesis from smoking.

In contrast to carcinogenic events, for non-carcinogenic events non-linear dose-response relationships, potentially with thresholds, are generally assumed based on the existence of protective and repair systems. From experimental toxicology, there are some indications for thresholds being involved in these diseases. For example, a threshold was determined for the accumulation of inflammatory polymorphonuclear leukocytes in the lungs of rat subchronically exposed to cigarette mainstream smoke with increasing concentrations of total particulate matter (see attached slide from our March 1, 2000, presentation to this committee: Kindt et al., unpublished). This assay is considered to be a surrogate marker for the inflammatory changes seen in cigarette smoke-related bronchitis. Another example for a mechanism-based threshold is the oxidative modification of blood lipoproteins in vitro: only after depletion of antioxidant vitamins with increasing smoke concentrations, the oxidative modification of lipoprotein components is initiated (Eiserich at al., 1995). Oxidative modification of the low density lipoprotein is considered a critical step in atherosclerosis (McCall and Frei, 1999). Most non-carcinogenic smoking-related health effects, such as the risk for chronic bronchitis or coronary heart disease, were also found to recover after smoking cessation (US DHHS, 1984 and 1989). For example, the abnormalities found in blood lipid profiles appear to reverse, at least in part, within weeks of smoking cessation (Stubbe et al., 1982). Also, the flow-mediated and endothelium-dependent peripheral arterial vasodilation, which is impaired by smoking, has been reported to be at least partly reversible after smoking cessation (Celermajer et al., 1993).

Conceptually, thresholds most likely exist for a number of mechanistic events in smoking-related diseases. However, practically these diseases develop in multiple stages (e.g., carcinogenesis) or parallel events (e.g., atherosclerosis and thrombosis) which makes it difficult to deduce thresholds for the overall disease outcome. In addition, these processes are triggered by exposure to a complex mixture of constituents, which may interact at various steps within the disease processes.

In summary, mechanistic considerations generally suggest that there are thresholds for smoking-related adverse health effects. However, thresholds or non-linear dose-response relationships have only rarely been found in epidemiological studies on cigarette smoking-related diseases, which can be related to the complex exposure and the complex disease processes as well as to the crude dosimetry employed. This situation might change for new products with less complex aerosol composition as well as with new tools that might be generated with improved exposure assessment as obtained from, e.g., our total exposure study (see answer to Question 7). Nevertheless, since the effects are dose-dependent, reduced exposure to the smoke constituents related to these effects are considered advantageous regardless of the presence of thresholds.

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Question #2: Do the filters in your cigarettes, including reduced-risk products under test-market or development, contain fibers? If so, can these fibers become airborne in the smoke inhaled by smokers? If so, to what extent does this occur? What is your estimate of the potential risk to human health from these fibers?

Response #2:

Philip Morris USA uses cellulose acetate fibers, paper fibers and polypropylene fibers in filter construction. In the United States, approximately 98% or more of the filters used on conventional cigarettes contain cellulose acetate fibers. The fibers are bound together with triacetin and wrapped with tipping paper.

The potential human health risk from exposure to cellulose acetate (CA) fibers is low since the probability of deposition in the lower respiratory tract is very low or zero. This conclusion is based upon expert opinions expressed in the scientific literature and experimental data generated by Collazo et al. (1999) that demonstrate that the aerodynamic diameter of cellulose fibers released from commercial cigarette filters is at least 22 □m and larger, too large to penetrate and deposit in the lower lung. High lung fiber burdens are commonly observed in normal healthy human lungs and may be associated with exposure to the environment and the large number of consumer products where fibers are used. CA fibers released from cigarette filters however are likely to deposit in the oropharynx and upper respiratory tract where they may be removed by normal clearance mechanisms.

Cellulose acetate fibers that may become airborne in cigarette smoke would only be present as a result of release from the filter tip end of the cigarette. Philip Morris USA has occasionally used an in-house laboratory method to evaluate the potential for fiber "fall out". Approximately 1 fiber/puff or less has been found when using this method. Cellulose acetate fiber release, CA fiber dimensions and respirability have been reported in the literature by scientific experts. The British Industrial Biological Research Association (BIBRA) reported that CA fibers released during sham-smoking (unlit) and machine-smoking of three commercial cigarette brands with different fiber diameters and filter tip construction was extremely low. Only one fiber was observed per 10 sham-smoked cigarettes. In machine-smoked brand B cigarettes, only one fiber was found from a total 30 cigarettes. In the tap test and during sham-smoking, A and B brands had the major proportion of released fibers between 100-600 □m. Brand C released a lower number of fibers but a wider range of fiber lengths under these conditions. Machine smoking increased the average fiber size and numbers present for brand A, particularly in the 500-600 and 1001-1101 □m size ranges, while the general pattern of fiber size distribution and numbers present remained unchanged for brands B and C (BIBRA International, 1996). Cellulose acetate fiber diameter was not reported in the BIBRA study.

Langer et al. (1988) conducted an extensive evaluation of the materials found in cigarette tobacco, ash, and smoke from seventeen commercial brand filter cigarettes and concluded that the materials were "adventitious soil particles or crystallization compounds formed during tobacco combustion" (Langer et al., 1998). Langer et al. did not report the presence of cellulose acetate fibers in mainstream smoke from any of the

tested cigarettes.

A fiber's potential to deposit in the lung is related to the fiber's dimensional characteristics, with fiber diameter being the most important predictor of aerodynamic size and potential for lung deposition by impaction and sedimentation. Fiber length is an important parameter with respect to interception by the airway surface (Witschi and Last, 1995).

Assessments of CA fiber diameter and potential for lung deposition have been reported in the literature and elsewhere. CA acetate fibers used in cigarette filters have a diameter varying from 20-60 □m (19). Inhaled fibers of this size have a very low probability of deposition in the human respiratory tract and an extremely low probability of deposition in the deep lung (Ashgharian and Yu, 1988; Timbrell, 1982). Esman and Erdal (1991) have stated, "the cellulose acetate material used in cigarette filters, fibers with circumscribed diameters of around 20-50 □m and theoretically with infinite length, are associated with a 'zero deposition probability' in the deep lungs. Not only are the fibers far too big to be deposited in the alveoli, but any lateral breakage of the fibers, if a fiber was damaged would also produce material that still has zero deposition probability because it still has the same diameter..."(Esman and Erdal, 1991). Walton (1991) states, "...the cut-point for a non-zero deposition probability (even using a very conservative aspect ratio of 5) in the deep lung would require the fibers to split length-wise into at least 3 fragments. It is clear that the cellulose acetate fibers used in cigarette filters could not be deposited in the deep lung" (Walton, 1991). Based upon the measured physical diameter of CA fibers used in cigarette filters and predicted lung penetration and deposition for such fibers, the probability of deposition in the lower respiratory tract is very low.

Recently, Collazo et al. (1999) reported on the use of an inertial impactor, designed in collaboration with V. A. Marple at the University of Minnesota (Collazzo et al, 1999a), for measurement of the aerodynamic diameter of airborne cellulose acetate fibers from commercial cigarettes (Collazzo et al, 1999b). The deposition site in the human lung for aerosols of each aerodynamic diameter has been well characterized by inhalation scientists such as O. G. Raabe and many others (Raabe, 1987). Using large cellulose acetate fibers, ranging from 20-50 □m in diameter and 75-1000 um in length, and released from cigarette filters, Collazo et al. demonstrated that approximately 2-10 fibers/cigarette were released and their aerodynamic diameters were always greater than 22 □m (Collazzo et al., 1999b). Using standard lung deposition models, the investigators concluded that the CA fibers are "non-respirable", they would deposit mainly in the oropharynx and were not likely to penetrate into the tracheobronchial region of the lung (Collazzo et al, 1999b). Based upon the experimental dosimetry work of Raabe (1987) in the mouth-breathing human, the probability of deposition of spherical aerosols with aerodynamic diameters of approximately 22 □m in the tracheobronchial region is expected to be very low, and pulmonary (alveolar) deposition would be even less likely (Raabe, 1987). From the work of Collazo et al., it appears that CA fiber deposition is only likely to occur in the upper respiratory tract where normal clearance mechanisms such as the cough reflex, mucociliary escalator, and swallowing would be expected to remove any fibers.

Currently, there are no scientific studies published in the literature that provide definitive evidence that cellulose acetate fibers from cigarette filters can penetrate to the deep lung in the human. On the contrary, theory, experts' judgement, and experimental data suggest that the large fiber diameter of CA fibers used to manufacture cigarette filters would severely limit the potential of these fibers to be inhaled or deposited in the tracheobronchial and alveolar regions of the lung. Deposition of fibers is likely only in the oropharynx and upper respiratory tract, where any deposited fibers may be removed by normal clearance mechanisms. Expert inhalation scientists have described the probability of deep lung inhalation and deposition of these CA fibers as extremely low or zero (Ashgharian and Yu, 1988; Timbrell, 1982; Esman and Erdal, 1991; Walton, 1991). However, Pauly and others claim that synthetic fibers found in the lungs of some smokers are derived from the cellulose acetate in cigarette filters (Pauly et al, 1995; Pauly et al., 1998)).

Natural and synthetic fibers are ubiquitous in our environment; normal healthy human lungs typically contain millions of fibers as a result of exposure to the environment (Roggli, 1990). For example, ordinary atmospheric pollution is likely to result in lung burdens on the order of 100,000 fibers per gram of wet lung tissue (Churg, 1983). High fiber counts in the lungs may also be related, at least in part, to the large number of consumer applications where fibers are used. According to Coggins (1995), "...CA fibers are manufactured in a wide range of shapes and sizes and are used in a large number of consumer applications including lingerie, dresses, blouses, robes and other apparel, linings, draperies, bedspreads, upholstery, carpets, umbrellas, formed fabrics, and cigarette filters" (Coggins, 1995).

The potential human health risk from exposure to CA fibers is considered to be low, since according to experts the probability of CA deposition in the mid and deep lung is very low or zero.

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Question 3: "What is the effect of removing a component or components of tobacco on the qualitative and quantitative composition of the new species of smoke? What is the empirical evidence that such alteration would be associated with reduced or altered disease incidence in humans?"

Response #3:

Removal of components has been attempted but has rarely resulted in a commercially acceptable product. They often resulted, as in the case of nicotine removal, in serious taste changes of the smoke of the modified cigarettes so that these products were not viable in the marketplace and, hence, no harm reduction was obtained. In other cases, e.g. nitrate, the significance for hazard reduction was unclear since the changes of biological responses could not be related to hazard reduction unambiguously. Most recent efforts, e.g., protein and TSNA, however, are promising.

Assumptions

In the strictest sense, the question should apply to components of the tobacco alone. However, "tobacco" is used in these comments as a synonym for the total filler of cigarettes; therefore, the following comments cover

- natural material in or on native tobacco and
- flavors and other ingredients added to the tobacco.

The phrase "qualitative and quantitative composition of the ... smoke" in the question we interpreted as referring to the

- biological activity (e.g., mutagenic activity in the Ames Assay) and the
- yield or concentration of the numerous constituents in the smoke.

These comments do not cover two other approaches that have been shown to alter cigarette smoke:

- selective filtration of the smoke in order to remove defined smoke components
- variation of the burning process, e.g., in electrically heated cigarettes, that has been shown to result in a biologically less active cigarette smoke (Terpstra et al., 1998)

Natural Material in or on Native Tobacco

Data on effects due to the actual reduction or removal of natural components of tobacco are scarce. The main reason for this might be that the removal of single target substances also affects other non-targeted substances and may have a profound effect on the taste of the resulting cigarette smoke, potentially leading to non-acceptance by the smoker.

- Nicotine

Driven by recommendations by the public health community and consumer research, Philip Morris USA developed and marketed in 1989 a cigarette with only residual amounts of nicotine in the tobacco. Early attempts in the 60's using solvent and steam extraction of nicotine were successful in removing nicotine but not successful in being selective for nicotine and maintaining acceptable taste characteristics. The development of a large-scale extraction procedure to remove nicotine from tobacco was achieved by supercritical fluid high pressure extraction with carbon dioxide, a technology based on the decaffeination process for coffee (used, e.g., by General Foods, which was acquired

by Philip Morris in 1985). The tobacco was treated in a commercial plant opened near Hopewell, VA, in 1989 and contained less than 0.2% of the original natural nicotine. No significant change in the genotoxicity (Ames activity) of mainstream condensates of denicotinized tobacco as compared to untreated reference tobacco was observed. In addition to nicotine, oils and waxes, isoprenoids, carboxylic acid, hydrocarbons, tobacco-specific nitrosamines, cembranoids, and stigmasterol were detected either in samples of the supercritical carbon dioxide used to extract the tobacco or from laboratory scale experiments. Several non-menthol and menthol brands (brand names NEXT and Benson & Hedges DENIC) with 9 mg tar and less than 0.1 mg nicotine (FTC) were test marketed in 4 test markets in 4 states starting end of 1989. After a strong marketing campaign those brands reached a retail share of up to 2.7% during the first 2 months after the launch. Their sales, however, declined rapidly in those test markets and the denicotinized brands were withdrawn after a year and a half. Consumer feedback indicated that major taste deficiencies of the denicotinized cigarette brands were the reason for low consumer acceptability. In laboratory settings the differences in consumers' perception were found not to be due to the lack of nicotine alone since adding back extracted materials including nicotine to test cigarettes did not restore the test cigarettes to the taste of comparable unextracted cigarettes. Another attempt to launch these brands was undertaken in 1991, mixing denicotinized and untreated tobacco in order to attempt to obtain better consumer acceptance. The second trial was also unsuccessful due to a continued lack of taste acceptance, and the production was stopped. Therefore, post-market exposure tests addressing concerns about the potential change of smoking behavior and cigarette consumption could not be undertaken. The total investment for these activities amounted to approx. 300 million USD.

- Nitrate

One of the examples in this area is the reduction of nitrate in tobacco. The concentration of nitrate has been shown to correlate directly with the formation of nitrosamines in smoke-an effect that can be explained by nitrosation, e.g., of tobacco alkaloids (Adams et al., 1984). The nitrate concentration in tobacco filler can be modulated by direct nitrate addition to the filler, by the use of different nitrogen-fertilized crops, different tobacco strains (e.g., bright tobacco low in nitrate and Burley high in nitrate), or tobacco that has been nitrate reduced, e.g., by nitrate crystallization. The effect of a modulation in nitrate concentration on the smoke chemistry is different for nitrosamines and polycyclic aromatic hydrocarbons (PAHs), e.g., B(a)P. While nitrosamines increase with increasing nitrate concentration, the PAHs decrease significantly. The difference between a high nitrate Burley and a low nitrate Bright is a factor of 15 or higher for the yield of both classes of animal carcinogens, but in different directions (Hoffmann and Hoffmann, 1997). As in smoke chemistry, the effect on biological activity also goes in different directions depending on the test system used. In the Ames assay with TA 98 as well as in a cytotoxicity assay with mammalian V79 cells, there was an increased biological activity with increased nitrate concentration (Roemer, 1990). The tumor formation in mouse skin after dermal application of smoke condensate (Hoffmann and Wynder, 1976) and induction of laryngeal cancerous and precancerous lesions after smoke inhalation (Dontenwill, 1973) were decreased with increased nitrate concentration.

- Protein

Recently a report on the partial removal of tobacco protein by water extraction and subsequent protease digestion was published. The condensate of smoke from these cigarettes showed a reduction in mutagenicity of 50 to 80 % in the Ames assay with tester strains TA98 and TA100 (Clapp et al., 1999) This is in line with the known high mutagenicity of protein and amino acid pyrolysates, pointing in the direction of heterocyclic aromatic amines as active agents (Matsumoto et. al., 1978). The data are corroborated by an increased Ames activity of cigarette smoke condensate when amino acids, especially tryptophan, are added to the tobacco (Tewes, 1992). Data on smoke chemistry, cytotoxicity, genotoxicity, general animal toxicity, and last but not least, of taste and resulting consumer acceptability of cigarettes with protein extracted tobacco have not yet been reported.

- Nitrosamines

Only very recently approaches used to reduce the formation of tobacco-specific nitrosamines (TSNAs) by more than 90 % have been reported. In Burley tobacco a microbiological nitrosation is considered to be the primary source and is reported to be prevented by microwave treatment of the tobacco that kills the bacteria (Day, 1999). For flue-cured tobacco this process seems of secondary importance. Here, N_XO_Y combustion gases of direct-fired burners in flue-cured barns appear to be mainly responsible for the formation of TSNAs. The use of heat exchangers instead of direct-fired burners thus may eliminate this primary source (Peele, Edwards, and Gentry, 1999). Further potential effects, other than the reduction of TSNAs, and especially further smoke chemistry and toxicological data have not yet been reported.

Flavors and Other Added Ingredients

During cigarette production flavors are added to the tobacco of American-blended cigarettes to enhance the taste of the smoke. Humectants are applied to the tobacco as a way to retain a certain amount of tobacco moisture of the cigarettes. In order to determine the potential effects of ingredients added to tobacco on smoke chemistry and biological activity of the smoke, cigarettes with and without the addition of ingredients have been investigated comprehensively.

When 333 ingredients (for technical reasons split into three groups) were added to American-blend commercial cigarettes at an approximate use level and at a multiple of the normal use level, an extensive chemical analysis of the resulting smoke indicated essentially no major changes. There were only isolated increases and decreases in constituents when compared to the control cigarette without the addition of ingredients. These changes, while statistically significant, were not supported by any biological changes. The mutagenicity as measured in the Salmonella Reverse Mutation (Ames) Assay was not increased nor was the cytotoxicity (measured in the Neutral Red Uptake Assay with mouse embryo BALB/c 3T3 cells). Also the inhalation toxicity determined in a 90-day inhalation study in rats (OECD protocol 413) with special emphasis on irritative changes in the respiratory tract was not increased. A few increases and decreases in some of the numerous endpoints were all well within the normal variation of such bioassays and considered to be due to statistical inference (Roemer et. al., 2000).

These data corroborate the findings of another rat inhalation study where over 170 ingredients were added in groups to 6 test cigarettes. The smoke from these cigarette

types showed no increase in the incidence of histopathological findings in the respiratory tract or the occurrence of new findings not already present in the groups exposed to smoke from the control cigarette without the addition of ingredients (Gaworsky et al., 1998).

Smoke condensate from cigarettes with and without the addition of ingredients to the tobacco was also evaluated for its carcinogenic potency in the mouse skin painting assay. When applied to the shaved back skin of mice, tumor incidence, latency, and multiplicity were essentially the same for the cigarette types with and without the ingredient (Gaworsky, 1999).

In summary, due to the limited amount of data to date, it is unclear whether the removal of protein, TSNAs, nicotine or nitrate is beneficial, either because of ambivalent test results, incomplete test results, or consumer acceptability. Flavors or other ingredients do not seem to give rise to a concern.

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Question 4: What are the criteria that should be used to assert that a specific form of tobacco or tobacco product is less harmful than others? What biomarkers should be used to assess the critieria?

Response #4:

A number of separate pieces of information are needed to make the assertion that a specific type of cigarette is less harmful than others. (See Figure 1.) The process would include a pre-market acceptability evaluation, which would involve smoke chemistry and both in vitro and in vivo toxicology testing to insure that a new product design change does not increase overall smoke chemistry or measured biological activity.

Once the product is on the market, an exposure assessment would be conducted. Due to the need for large numbers of smokers who currently use a product as their brand, it would be best to conduct this study in an after-market environment. (See the response to Question 7 for more information about exposure measurement, including biomarkers of exposure.) It may be that additional testing of a specific health endpoint is needed relevant to a proposed claim. This additional testing would be conducted in animals or cell culture systems and would be directed toward specific health endpoints not extensively evaluated in the standard acceptability test battery. (Please see the response to question 6 for more information about these tests). By combining the information from the exposure assessment and the acceptability tests and any specialized harm reduction tests, it would be possible to make a provisional claim about the product as having reduced-risk characteristics (e.g., this product has reduced carbon monoxide).

A further step toward the assertion that a particular type of cigarette is less harmful would be the assessment of short-term (after one year or less of use) health effects in humans. This testing would typically be conducted to assess the potential for changes in long-term (following 10 years or more of use) effects. Suggestions for biomarkers of effect for the chronic diseases associated with smoking are discussed in the response to Question 6. Once an adequate data set is complete at this stage, a product claim could be made (e.g., this product <u>may</u> reduce your risk of cardiovascular disease as compared to other cigarettes).

Following the completion of long-term studies in humans, a provisional claim could be confirmed (e.g., this product <u>will</u> decrease your risk of cardiovascular disease as compared to other cigarettes). Due to the long time needed to reach this confirmation, it would be important to allow the earlier provisional claim as guidance to consumers using the information discussed above.

The claims made regarding harm reduction at any of these stages should be made based on well-designed studies (including quality assurance and validated methods) with results that are appropriately analyzed and biologically relevant. Preferably, the endpoints measured would have a plausible link to the human health effect of interest.

Question #5: What is the appropriate comparison product for reduced-risk products? A Kentucky reference cigarette? The leading product as assessed by market share? The lowest-risk product currently available? Each individual smoker's brand at time of switching to the new product? Each individual smoker's dominant brand of his/her smoking history?

Response #5:

The appropriate comparison cigarette depends on the type and objective of the study.

For studies of smoke chemistry and toxicology, the key purpose of the comparison cigarette is to provide an anchor point. Any cigarette compared to this anchor point could thereby be compared to each other. In this regard, the University of Kentucky reference cigarette 1R4F (Tobacco and Health Research Institute, 1990) is suitable at this time. This cigarette was produced in a single manufacturing run in 1983. The construction of this cigarette is representative of products in the U.S. marketplace. Additionally, Steele et al. (1995) found that the mutagenic activity of the 1R4F cigarette is in the middle of the activities for brands in the U.S. marketplace consistent with its tar delivery. The chemistry data derived in the Massachusetts benchmark study also shows that the 1R4F cigarette behaves similarly to brands representing the full range of cigarette construction parameters in the U.S. marketplace (Tobacco Industry presentation to the State of Massachusetts, Department of Health, 2000) and generally this relationship held under FTC and exaggerated smoking conditions. Since the mutagenic activity and smoke chemistry yields fall in the middle of those for brands in the U.S. marketplace and are equivalent on a tar delivery basis, the use of the 1R4F cigarette as a comparison provides information relevant to the market as well as a benchmark for comparison among studies. We are currently extending the work on the comparison of the University of Kentucky reference cigarettes in comparison to commercial brands. These tests will include reference cigarettes (e.g. 1R4F) and commercial products under different smoke collection conditions. In addition to smoke chemistry, the smoke will be tested in the Ames test and mammalian cell cytotoxicity tests. The results of these experiments will help guide our future use of the 1R4F reference cigarette.

For human studies of either exposure or health effects, commercially available cigarettes would be preferred to the University of Kentucky reference cigarettes. These Kentucky reference cigarettes are not flavored and have very different subjective characteristics than commercial products and would therefore not be suitable for the extended smoking period that would be required in such studies. In choosing a market cigarette for a reference, one must consider whether the reference point for harm reduction is on a population basis or individual basis. Regarding the use of commercial brands, here are some brief observations:

- Perhaps a population-based reference would be most useful. This might include the Massachusetts benchmark study, the additional biological data we are adding which is mentioned above, and actual exposure data such as we are planning in our total exposure project (presented to the IOM in February).

- Using any single brand has the issue that that brand could be changed over time such as reducing tar delivery.

- Trying to use the lowest-risk product currently available may have a difficulty. No one product may be the lowest risk product for all endpoints. Characteristics of one product that may make it lower risk for cardiovascular effects may not affect other disease risks. Another product might address cancer but not other risks.

- Trying to use each individual smoker's dominant brand of his/her smoking history may have considerable variability. One source is the possibility of a change over time such as reducing tar delivery.

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Question #6: What endpoints would you recommend for assessing harm reduction through use of reduced risk products or by decreasing consumption of existing products via use of nicotine replacement therapies or other pharmaceutical products?

Response #6:

For a complete assessment of the potential for harm reduction, the harmful effect, its dose-response relationship, and the exposure in the respective situation need to be identified. Since exposure assessment will be dealt with elsewhere (Question #7), this response will solely deal with surrogate endpoints to assess the effects and their dose-response relationship in surrogate models. It should be clear that the extent of testing to support a claim on harm reduction exceeds what is required in terms of acceptability testing for market introduction of changes in cigarette design or ingredient additions. (See Figure 1.) Although there is some overlap, in the following we will focus on endpoints related to harm reduction testing.

We consider four tiers of endpoints to be useful to assess the potential for harm reduction:

- chemical analysis of cigarette smoke,
- experimental toxicology,
- clinical tests, and
- epidemiology.

With the exception of the first tier, these should be applicable to both types of harm reduction strategies, i.e., for reduced risk products as well as for decreased consumption of existing products in combination with pharmaceutical products. It should be mentioned that to our knowledge there are no precedents for the assessment for harm reduction in the case of using pharmaceutical products, such as nicotine replacement therapies, in combination with a reduced consumption of existing products. As a preliminary statement, based on Dr. N. Benowitz' lecture to this committee on nicotine pharmacology and toxicology, toxic effects of nicotine by itself seem to be very limited and are no more than those of cigarette smoking (for cardiovascular endpoints, see also Benowitz and Gourlay, 1997).

The assays used to assess the potential for harm reduction should be related to the mechanisms of the smoking-related diseases. They need to be validated, e.g., based on the recommendations of the International Congress of Harmonization, at least to the degree of reproducibility within and between laboratories. They should provide quantitative data in order to allow dose-response evaluations.

<u>Chemical Analysis of Cigarette Smoke</u>

We suggested analyzing a list of smoke constituents that is based on the 1993 recommendation of the Consumer Product Safety Commission and extended towards known smoke constituents that have been classified by IARC as group 1, 2A, or 2B carcinogens (Voncken et al., 1998). This extension was deemed prudent based on the current lack of an established inhalation carcinogenicity model for cigarette smoke (vide infra). Our current list comprises more than 50 smoke constituents. Similar lists have been suggested by others (Vorhees et al., 1997; RJR, 1998).

With this number of endpoints, there will be increases in yields of certain constituents in parallel to decreases in others. The results of these divergent changes in the chemical composition need to be consolidated with a sound toxicological procedure so that new products that show advantages in many endpoints will not be abandoned because of an unfavorable outcome for a few less relevant endpoints. We are currently working on such a procedure.

Experimental Toxicology

Most currently used experimental endpoints in routine cigarette smoke toxicology are directed towards chemical carcinogenesis.

We have adopted the recommendations of the International Congress of Harmonization (ICH) to assess the genotoxicity of cigarette smoke. This recommendation includes a bacterial mutagenicity assay, a mammalian cell mutagenicity or clastogenicity assay, and an in vivo genotoxicity assay. We have routinely been using the Salmonella typhimurium reverse mutation assay with 5 tester strains in the absence and presence of a pro-mutagen activation system. For the assessment of harm reduction, however, only those assay variants responding to cigarette smoke can be used, i.e., mainly strains TA98 and TA100 in the absence and presence of the activation system (Roemer et al., 1998). As a mammalian test system for in vitro genotoxicity, we use the mouse lymphoma assay, which covers both mutagenic and clastogenic endpoints of genotoxicity but in our hands shows less discriminatory power when comparing different cigarette types than the bacterial assay. To our knowledge, there is no in vivo genotoxicity assay available that reproducibly responds to cigarette smoke. While a number of publications have been published on the activity of cigarette smoke to induce bone marrow micronuclei in mice or rats (Balansky et al., 1999), we as well as others (Lee et al., 1990) were not able to reproduce these findings, even under extreme testing conditions. Other in vivo assays have been suggested but not routinely and reproducibly applied to cigarette smoke, e.g., cytogenetic changes in alveolar macrophage (Rithidech et al., 1989; Balansky et al., 1999). There are potential other assays that need to be evaluated for their use with cigarette smoke, e.g., the Comet assay for target cells or surrogate cells (peripheral lymphocytes) ex vivo or transgenic rodents engineered as ex vivo genotoxicity models.

Because of the decreasing relative risk for lung cancer after smoking cessation (US DHHS, 1989), we consider assays important that are considered to assess the promotion phase of carcinogenesis. Exposure of rodents to cigarette smoke as well as other irritant inhalants generates regenerative hyperplastic responses in the epithelia lining the respiratory tract, which are reversible upon cessation of exposure (Coggins et al., 1989). These as well as the metaplastic changes observed in subchronic inhalation studies can be considered surrogate assays for the promoting potency of cigarette smoke. As an in vitro model, cytotoxicity assays for both the total particulate matter and the gas phase of cigarette smoke have been routinely used (Tewes et al., 1998). Other in vitro assays that were recommended to assess the promoting activity of cigarette smoke are the gap-junctional communication (Rutten et al., 1988) and 2-stage transformation assays. In our experience, the latter assay responds to cigarette smoke, however, with a poor dose-response characteristic and a poor discriminatory power (Schlage et al., 1999), and thus are not considered useful to quantitatively assess the potential for harm reduction.

Carcinogenicity studies using inhalation exposure of rodents to cigarette smoke have not been successful in generating lung tumors (Coggins, 1998). Recent efforts to improve this approach have aimed at optimizing the dose (Lovelace Respiratory Research Institute (LRRI), 1995), the sensitivity of the detection of tumors (Stinn et al., 1999; Friedrichs et al., 2000), or on using a model that has a high spontaneous background to lung tumor formation (Witschi, 1998) but has previously not been used for regulatory purposes. While the other studies have not yet been reported in detail, the Witschi model has some mechanistic issues that need to be resolved before it can be used for routine testing for harm reduction. As a substitute model to produce epithelial tumors from a cigarette smoke fraction, i.e., condensate, mouse skin painting has been performed (Roemer and Hackenberg, 1990; Meckley et al., 1999). Since this model does not administer the whole smoke by inhalation and studies tumors at a non-target site, we consider it as useful to answer specific mechanistic questions but not sufficiently relevant for routine testing.

Experimental surrogate assays that would be specific for non-carcinogenic endpoints have not routinely been used for assessing cigarette smoke. Some information could be obtained by evaluating the organs specified in the OECD guideline no. 413 (1981) in the course of a subchronic inhalation study. For example, representative sections from the heart and aorta as well as from urogenital organs have been evaluated beyond the organs and tissues of the respiratory tract. Only some changes in organ weight (liver, heart, adrenals, thymus, depending on the exposure schedule) with no histological correlates have been observed in studies using rats, with no indications of, e.g., emphysematous or atherosclerotic changes. A large number of assays has been used as investigative tools but not for routine testing of cigarette prototypes. These assays thus currently lack the validation that would be required for their application to test for potential harm reduction.

For cardiovascular disease endpoints, atherosclerosis, vascular tone changes, and coagulopathy are the presumptive major mechanistic effects involved. A number of in vitro, ex vivo, and in vivo tests have been used to mechanistically study the effects of cigarette smoke and might be applicable upon further validation for routine testing. Here we can only provide some examples that might be considered for further investigation and potentially validation, i.e., the in vitro oxidant challenge of plasma lipoproteins with cigarette smoke (Eiserich et al., 1995), the ex vivo vasodilatory effect of acetylcholine in isolated blood vessels (Hutchison et al., 1997), the atherosclerosis in ApoE-deficient mice after subchronic exposure (Breslow, 1996; Gairola and Daugherty, 1999), and the leukocyte aggregation and adhesion to endothelium in acutely exposed hamsters (Lehr et al., 1994). These endpoints are considered to be mechanistically related to the effects seen in human smokers.

The database for experimental reprotoxicological endpoints is relatively small. We are not aware of any test on cigarette smoke that is based on international guidelines for reproductive toxicology studies. An extended literature search is currently being performed to determine the smoke-related effects in humans and their potential experimental surrogates.

Chronic obstructive pulmonary diseases are characterized by pulmonary inflammation, the obstruction of airways by mucus and morphological changes, and emphysema. Surrogate endpoints are being established to assess these effects both in vitro and in vivo. The rat responds to subchronic cigarette smoke inhalation with a bronchoalveolar accumulation of polymorphonuclear leukocytes and macrophages which is similar to the disease symptoms in human smokers (Kindt et al., unpublished; Mauderly et al., 1989). A chronic mouse emphysema model has been suggested by March et al. (1999) and needs further evaluation. As an in vitro surrogate, the emphysematous disturbance of the protease/anti-protease balance in the lungs can be assessed (Pryor et al., 1990). This endpoint might also be assessable ex vivo.

Clinical Tests

For the purpose of supporting potential claims on harm reduction in the future, we consider clinical tests or biomarker studies of effect necessary to some extent (see flow chart attached to response no. 4). These tests should be performed based on internationally accepted guidelines (e.g., Helsinki convention, International Congress of Harmonization, Good Clinical Practice). Solid exposure assessment and control of compliance with the study design is an absolute pre-requirement. (See Question #7).

In general, one might differentiate between acute (minutes to days) and short-term (weeks to months of use of the new product) tests. Also, the degree of invasiveness of the assays needs to be considered. The following list of potential assays should be considered explorative and by no means conclusive, and needs to be further evaluated based on literature reviews and collaboration with other researchers.

A number of acute markers for carcinogenicity have been suggested. Urinary mutagenicity has been considered a measure of exposure and activation/deactivation of mutagens and pro-mutagens (Bartsch et al., 1990). Acute genotoxic effects have been suggested to be assessed by cytogenetic changes in peripheral lymphocytes (chromosomal aberration, sister chromatid exchange; single cell electrophoresis for DNA breaks) (Van Maanen et al., 1994; Poli et al., 1999). Likewise, these genotoxic effects could be assessed using free or exfoliated cells from the bronchoalveolar space, obtained either by lavage or induced sputum samples. However, while bronchoalveolar lavage might be considered relatively invasive, induced sputum analysis seems to be promising but needs further investigation.

The latter cells could also be used for assays indicative for relatively later changes in the process of pulmonary carcinogenesis, such as loss of heterozygosity or mutations in proto-oncogenes and tumor suppressor genes (Wistuba et al., 1997; Kelloff et al., 2000; Welsh et al., 2000). However, these genotoxic effects seem to persist for many years after smoking cessation. Since the relative risk for lung cancer decreases with duration of smoking cessation (US DHHS, 1989), genotoxic events may be less useful than potential markers for promotion to assess the efficacy of using reduced harm strategies. We are not aware of any clinical endpoint that would allow the determination of morphological changes associated with reduced promotion of lung tumorigenicity except biopsy.

For cardiovascular effects, degradation products of thromboxane and prostacycline could

be determined in urine after acute exposure (Wennmalm et al., 1991). Also, platelet aggregability and monocyte/endothelial adhesion could be assessed (Adams et al., 1997). The ratio of high density and low density lipoproteins seems to react fairly quickly to smoke exposure (Freeman et al., 1993). Flow dynamic changes may also be assessed.

In addition to respiratory changes, which reverse with smoking cessation (US DHHS, 1989), chronic bronchitis may be assessed by analyzing cells or cytokines in bronchoalveolar lavage or induced sputum, with the restrictions as mentioned above. It remains to be determined whether an impaired protease/anti-protease balance can also be analyzed in these media (Fera et al., 1986; Gadek et al., 1979; 1981).

Since no regulatorily accepted and validated assays in the sense of experimental toxicology are currently available for the clinical testing to support the claim for reduced harm tobacco products, flexible and scientifically reasonable approaches are needed to support such a claim, and a broad scientific consensus needs to be established in every single case.

Epidemiology

We consider epidemiological studies necessary to follow up on newly introduced products that claim reduced harm. Data from these studies will provide the final evidence for harm reduction and can be used to further validate previous pre-clinical and clinical studies. Epidemiological studies are also needed to make sure that, while one adverse effect decreases as intended, no other adverse effects increase or newly arise.

Summary

We consider four tiers of endpoints to be useful to assess the potential for harm reduction: chemical smoke analysis, experimental toxicology, clinical tests, and epidemiology. These tiers go beyond what currently is considered necessary for market acceptability testing. Chemical smoke analysis and experimental toxicology should be performed before any test marketing. Clinical test would be performed after market introduction in order to support provisional product claims. Epidemiology is only possible long after market introduction to confirm product claims. Endpoints for chemical smoke analysis and experimental toxicology endpoints in the context of carcinogenicity are available and being routinely used, while they need to be further validated for non-neoplastic diseases. For clinical tests, there is no common understanding regarding the choice of endpoints, and a flexible and scientifically reasonable approach is needed to obtain consensus among the stakeholders. Epidemiological data are needed on the long run to ascertain the intended harm reduction and to further validate experimental and clinical testing strategies.

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Question #7: What clinical exposure data in humans do you feel is important or even necessary for evaluation of a new product (smoked and smokeless[1]) before it is marketed? Please be specific with respect to number of subjects, length of use, biomarkers measured and test conducted.

Response #7:

We believe that as long as a new product does not increase the hazard of smoking, it should be allowed into commercial sales. However, before any claim of reduced harm is made, human exposure measurements are an important component of data relevant to supporting such claims. (See Figure 1.)

In fact, there are some significant factors which require market introduction prior to obtaining exposure data.

- Ensuring that the appropriate number of smokers are available for the studies is one. A multitude of factors result in a requirement for large sample populations for statistically meaningful exposure measurements; these include the qualitative complexity of cigarette smoke, the low levels at which many of those constituents are present, the possibility of numerous metabolites in human fluids for each of the constituents, and significant variation in the distribution of these metabolites for different individuals. Uncontrolled clinical trials are appropriate for evaluation of biomarkers of tobacco smoke exposure since it can be assumed that subjects maintain their usual smoking behavior (Scherer, 1999).

- A second factor is that the transient smoking behavior changes associated with use of a new cigarette require that the new product must be used for an appropriate timeframe before valid exposure measurements can be conducted.

As described to the IOM in March, the Philip Morris total exposure project is a major study incorporating biomarkers of exposure to assess the exposure of smokers to existing cigarette products. These data could be used as a population baseline for future product exposure studies.

Population size. Factors that enter into play when an appropriate sample size is being determined include magnitude of the difference in biomarker level and variations in those differences, the parameter of interest, and the effect size, power and the level of significance [Fayers and Machin, 1995]. Recent evaluations based on the measurement of nicotine and five of its metabolites in urine [Byrd et al., 1995, 1998] indicated that a sample size as large as 4,500 to 6,000 would be needed to determine statistically significant differences. New product smoker populations of these sizes will not be obtainable in a pre-market situation.

Length of time of use of new product. The only practical way to evaluate harm reduction of new cigarette products is by comparison. These comparisons could be between two populations of subjects or between subjects before and after changing to a different product. Experimental brand-switching studies comparing biomarkers of tobacco smoke exposure in subjects smoking existing cigarette products and reduced harm designs have to take two major factors into consideration. Those factors are: (i)

transient compensatory smoking behavior will occur in subjects on brand switching [Scherer, 1999], and (ii) the biological half-lives of the biomarkers to be assessed will determine the time period which has to elapse after switching cigarette designs before comparative sampling can be performed. The recommended time period that has to elapse after smoking of a new cigarette commences is four times the half-life of the longest-lived metabolite. For the biomarkers outlined below, a minimum elapsed time of 6 months would be required. Furthermore, to avoid intra-individual variation in biomarker levels, multiple sampling techniques have to be performed for all subjects smoking both cigarette designs.

Biomarker selection. Based on current scientific knowledge of the composition of mainstream cigarette smoke and the metabolism of some constituents of mainstream cigarette smoke both in humans and laboratory animals, certain smoke constituents can be selected which should serve as biomarkers. Three basic criteria have to be met: (i) specificity of the biomarker, (ii) sensitivity of the analytical methods of detection, and (iii) understanding of the human metabolism and pharmacokinetics of the biomarker and/or its metabolites [Benowitz, 1999.] We add to this the criterion that biomarkers representative of both gas and particulate phase smoke constituents must be utilized.

Tests conducted. Employing the above criteria as guidelines, the following biomarkers can be used: nicotine metabolites in urine: urinary nicotine plus the nicotine-derived metabolites cotinine, trans-3'-hydroxycotinine, nicotine-N-glucuronide, cotinine-N-glucuronide and trans-3'-hydroxycotinine-O-glucuronide [Benowitz et al., 1994]; CO in exhaled breath and carboxyhemoglobin (COHb) [Scherer, 1999]; hemoglobin adducts of the aromatic amines 3- and 4-aminobiphenyl [Bryant et al., 1988]; acetonitrile in exhaled breath; and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) metabolites in urine [Hecht and Tricker, 1999]. Most of the analyses for the selected biomarkers are based on chromatographic/spectrometric techniques.

In summary, the first step in a responsible approach to testing of reduced harm cigarette products will be the conduct of the pre-market acceptability testing to insure that the design change does not increase the overall smoke chemistry and measured biological activity. Once the cigarette is marketed, and prior to harm reduction claims, human smoker exposure measurements will be acquired and evaluated. The variability in the conditions under which cigarettes are naturally used and the requirements for very large populations for statistically meaningful results require that exposure measurements be conducted post-marketing.

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Question #8: If a goal is to develop a reduced-risk product that is still attractive to smokers who wish to continue smoking, what research agenda would you recommend? What do you need to know to accomplish this that you do not know already? Consider same question for smokeless tobacco products and comment on the possibility suggested by Swedish Snus that taste can be maintained while risk is minimized.

Question #12: What is your thinking on the design of a population-based study to assess the effects of the introduction of a reduced-risk product on risk perception of tobacco use and on tobacco initiation, cessation, or relapse?

It is difficult to consider developing an answer to Questions #8 and #12 without considering how they impact one another. It is desirable to develop a consumer acceptable, reduced harm product. In so doing, an important component following the market introduction of reduced harm products is post-market surveillance to assess the effects of the introduction of the product on risk. This surveillance would be incomplete without provisional product health claims in place during the monitoring. For this reason, we have combined the answers to Questions #8 and #12 in this section.

Response #8:

A reduced harm product that is unacceptable to the consumer is of little value (US DHHS, 1981). It does not advance our harm reduction efforts, does not benefit the public heath community that hopes to transition inveterate smokers to a reduced harm product, and does not benefit the consumer, who stands to directly benefit from such a product. Therefore, to be commercially viable and to accomplish the goal of providing harm reduction to that population of smokers who do not quit, any new reduced harm product must possess characteristics that smokers deem to be desirable.

For example, tar delivery, sensory impacts, psychosocial factors, and perceived benefits must be addressed. This general description reflects what is represented by "subjective testing" in Figure 1. At Philip Morris, a design panel, composed of a small but diverse population of Research, Development & Engineering (RD&E) staff, is developed. This panel may be responsible for total design and implementation, or may only be responsible for correcting potential sensory defects. This group develops prototypes that possess the desired design parameters and conducts the preliminary sensory evaluation. This process ensures that the prototypes meet any sensory or design objectives defined, can be relatively extensive, and may require several cycles of redesign.

Following acceptance at this phase, the prototype goes to a larger in-house descriptive panel. Feedback from this panel may also produce design changes which affect prototype production. From here, the prototype could move to an external, larger scale product-testing situation. Feedback from this large group of smokers provides the most realistic evaluation of the sensory acceptability of this new product relative to its design parameters or to existing product.

At this point, decisions would be made as to the suitability of launching the prototype as

a new product. However, with a reduced risk product, additional considerations might have to be made. (See Figure 1.) It is conceivable that any process used to reduce the risk of a new product might result in the introduction of uncorrectable sensory defects. In this case, consumer-testing studies would have to be conducted to determine whether consumers would actually accept the tradeoff of reduced risk benefits for any sensory deficiencies that might be inherent in the product.

In summary, Philip Morris would utilize our in-house process to guide the development of reduced harm products. We will use our expertise to produce the most consumer acceptable, low risk products possible. In guiding and evaluating reduced harm, we would enlist the support of Scientific Advisory Boards. Our existing testing programs will be utilized to detect and address sensory deficiencies. Logically, we would institute research programs designed to enhance consumer acceptability of deficient products on a case by case basis.

Response #12:

Studies have been conducted (ref - smoking, milk products, fast food, etc.) which demonstrate that products that purport to be of reduced risk impact the perception of risk and thus the consumption of that product (US DHHS, 1989; Rickert et al., 1988). One needs to look no further than low fat milk, air bags or "lite" fast food. It reasonably follows from this, that if a tobacco product were to be introduced and marketed with reduced-risk claims, perception of actual reduced risk with this product may impact consumer use of the product.

Referring to Figure 1, any impact on smoking incidence would be accounted for in population data collected after a provisional claim is made. The real concern is not simply the impact of reduced harm products on perception, one motivational aspect of behavior, but rather on the risk realized by the population. For example, if the actual risk of a product is reduced by 75% but the population utilizing the product increases by 10-20% because they perceive it to be less risky, public health would still be served.

While a goal in the efforts to protect public health would seem to be to reduce the number of people utilizing hazardous products, the ultimate goal would be to decrease the population risk. Long-term post-market surveillance studies would evaluate the accomplishment of this goal. These types of studies are, we believe, beyond the scope of this written reply. In fact, this topic could constitute a collaborative effort with appropriate scientific bodies. However, we can comment in general on the various aspects, which our experience demonstrates should be considered or controlled for to ensure validity of the results. These studies could be carried out at an appropriate point in time following the introduction of any reduced risk claims.

These would include, but would not be limited to:

- Selection of Appropriate Controls
- Selection of Population Size
- Selection of Study Length
- Identification of Methods of Assuring Validity of the Results
    - Consumption Indices
    - Exposure Monitoring

    - Biomonitoring
- Identifying Appropriate Sources of Data
- Development of Appropriate Survey Instrument
- Development of Population Harm Reduction Equation
- Inclusion of Appropriate Quality Control Elements
- Appropriate Peer Review

Of these items in particular, the development of an objective harm reduction equation would seem to be the most important. It is anticipated that this equation would rationally relate changes in actual hazard, as determined by any and all bioassays employed, with changes in smoking incidence for a new reduced harm product versus its appropriate control (hazard + exposure = risk).

In summary, population based studies you ask about have one critical design feature- they must include expressed reduced harm claims in order to determine the overall impact on the population of introducing a reduced harm product.

References

Question #8:

U.S. Department of Health and Human Services (1981). The Health Consequences of Smoking, The Changing Cigarette, a report of the Surgeon General. Rockville, MD.

Question #12:

Rickert, W.S., Robinson, J.C., and Lawless, E. (1988). Limitations to Potential Uses for Data Based on the Machine Smoking of Cigarettes. Independent Scientific Committee on Smoking and Health Symposium, Nicotine Smoking and the Low Tar Programme. Oxford Press, London, England, pp. 85-89.

U.S. Department of Health and Human Services (1989). Reducing the Health Consequences of Smoking, 25 Years of Progress, a report of the Surgeon General. Rockville, MD.

Question #9: What is the extent of your plans for internal or external activities in supporting health outcomes studies for your products? Particularly, do you support or plan to support epidemiological or related investigations?

Response #9:

Our current plans in this regard center mainly on exposure assessment as described in the answer to Question #7. We are currently considering, as well, the evaluation of short-term, less than one year, health endpoints in human studies. These studies would be conducted as endpoints are identified that are plausibly predictive of chronic disease. While we will be pursuing this area of research, the limiting factors are guidance from and cooperation of the public health community, as well as regulatory guidance. Reduced harm products, which are deemed so only by industry scientists, not communicated to the consumer, and therefore not used, will be of no value. Hence, our definitive plans will follow the lead of the public health community and regulatory bodies. That is why our efforts are focused on supporting groups such as this IOM Committee in working through these questions.

Question #10: What might be the best mechanism to foster collaborative studies between tobacco industry, university, and other scientists?

Response #10:

Important ingredients for collaborative interactions between the tobacco industry, academia and government and non-government scientists are open and frequent communication, rigorous scientific peer review of scientific work, and transparent processes for both funding and scientific review. These are the tools with which trust will flourish.

We are a willing participant of such interactions and bring talented research resources and expertise to such communication and collaboration. It is now Philip Morris USA's written mission statement to be the most responsible, effective, and respected developer, manufacturer, and marketer of consumer products made for adults. In doing so, we follow written company values of integrity, trust and respect, executing with quality, and sharing with others.

An expression of the ethical principals that these tools will support have been adopted by many professional scientific organizations. An example is the first three statements taken from the Code of Ethics of the Society of Toxicology (Society of Toxicology, 2000):

- Strive to conduct their work and themselves with objectivity and integrity.
- Hold as inviolate that credible science is fundamental to all [toxicological] research.
- Seek to communicate information concerning health, safety, and toxicity in a timely and responsible manner, with due regard for the significance and credibility of the available data.

Regarding these tools:

Communication

Scientific information generated by any of the groups you mention should be disseminated as widely as possible through scientific meetings, colloquia organized jointly between industry and non-industry scientists, informal dialogue, and publications. This meaningful communication should focus on the scientific issues involved in the development of reduced harm products.

Peer Review

Scientific results must be published in peer-reviewed journals. In some instances, an obstacle which must be overcome is a non-scientific policy which some journals and organizations currently have where tobacco industry scientists are not allowed to publish in their journals. The only criterion for publication should be the scientific quality of the work.

Transparent and Open Processes

Transparent processes for determining funding criteria and judging the merits of a research proposal or research report should exist and be made public. This applies for all organizations, including the operating guidelines of our own external research program. It may be important to note that at Philip Morris USA any funded investigator has the clear right, and expectation, to publish his/her findings. That investigator has

total control over the content of such publications. We do have one requirement, however, that all work that we support financially contains an attribution of our financial support.

References

Society of Toxicology (2000). Code of Ethics. In: Society of Toxicology website: http//www.toxicology.org.

Question #11: What roles should various sectors (e.g. industry, academia, government, foundations) play in the design, funding, oversight, reporting, and modification of post-marketing surveillance of newly introduced reduced risk products?

Response #11:

Each of these groups has a critical role to play-the industry should invest whatever resources are necessary to design and commercialize reduced harm products. Academia and scientific bodies should critically review the methods and evidence the industry used to assess these products. Government should insure that any claims the industry wants to make are scientifically sound and consistent with good public health policy. All of these groups should in a collaborative manner be involved in studies to do research on the health concerns.

The goal of the post-market surveillance studies is to confirm that the newly introduced reduced harm products do indeed contribute to a reduced risk. The studies should be designed to evaluate the end points associated with any proposed claims regarding harm reduction. It is imperative that the studies be well designed and controlled and that the test hypothesis is agreed to by the relevant stakeholders prior to the start of the studies. The tobacco company should take the lead role in post-market surveillance studies; however, the process cannot work without clear and open communication and collaboration between the stakeholders. The design, execution, modification, and reporting of post-market surveillance studies will have participation from all of the stakeholders you mention. Independent oversight is an important part of any rigorous scientific process.